APPENDIX

APPENDIX

[LOGO]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

[Jul. 22, 1981]

Bruce B. Pharriss, Ph.D.
Vice President of
Scientific Affairs
Collagen Corporation
2455 Faber Place
Palo Alto, California 94303

Re: P800022
Zyderm™ Collagen Implant
Filed: May 2, 1980
Amended: November 10, 1980
February 24, March 19, April 10,
April 16, and May 7, 1981

Dear Dr. Pharriss:

The Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) for the Zyderm™ Collagen Implant (hereinafter referred to as Zyderm™). The PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin production and marketing of the device upon receipt of this letter.

FDA will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. In addition, the notice will state that a copy of all approved final labeling (which may be a draft of the final labeling) is available for public inspection at the Bureau of Medical Devices. Within thirty days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may obtain review of this decision by requesting an opportunity for administrative review, either through a hearing or

review by an independent advisory committee under section 515(g) of the Federal Food, Drug, and Cosmetic Act.

FDA approval is subject to full compliance with the conditions described in the enclosure and the following:

1. The sale, distribution, and use of this device is to be restricted to prescription use in accordance with 21 CFR 801.109.

2. The post-approval (Phase IV) studies under your immunology protocol ZC-980 shall be extended from 3 to 12 months, and shall include determination of antibody levels in patients at 6 and 12 months after initiation of Zyderm™ treatment and the results submitted in the annual report. The studies shall report experimental details, such as the frequency and the amount of Zyderm™ injected, and the dates of blood sample collection from each patient. Patients selected under this protocol shall represent a cross section of patients receiving Zyderm™.

   In addition to Zyderm™, native and denatured bovine skin type I collagen (not treated by pepsin) shall be used to determine the levels of anti-Zyderm™ antibodies in the patients.

   Data on the cross-reactivity of Zyderm™ antibodies with type III collagen shall be provided, since human skin contains both type I and type III collagen.

   Circulating Zyderm™-antibody complexes shall be determined in fresh blood samples, and their levels demonstrated to be in the same range as those from individuals not exposed to Zyderm™ treatment.

3. In the post-approval (Phase IV) period, Zyderm™-treated patients shall be monitored for the occurrence of adverse reactions at 6-month intervals during a 3-year period, and the follow-up data submitted in the annual report to the FDA.

FDA will review these data and determine whether or not the post-approval monitoring of Zyderm™ should be continued at the present level.

4. A patient information manual shall be distributed with the device.

All stated requirements are subject to change upon publication of a final premarket approval procedural regulation. Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a product which is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

All required documents must be submitted in duplicate to the Bureau of Medical Devices, Document Control Center (HFK-20), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

If you have any questions concerning the approval of this application or its conditions, please contact Carl A. Larson, Ph.D., at (301) 427-7156.

Sincerly,

/s/ Robert G. Britain
for VICTOR ZAFRA
Acting Director
Bureau of Medical Devices

Enclosure

Conditions of Approval

Approved Labeling. As soon as possible, and prior to commercial distribution of your device, submit two copies of all approved labeling in final printed form.

Advertisement. No advertisement for this device shall recommend or imply that the device may be used for any use that is not mentioned in the approved labeling for the device. All written promotional material shall state the indications, contraindications, warnings, precautions and adverse effects of the device.

PMA Supplements. Before making any change that may affect the safety or effectiveness of the device, submit a supplemental PMA for review and approval by FDA. Such changes include, but are not limited to:

(1) new indications for use;

(2) labeling changes;

(3) changes in manufacturing facilities, methods or quality control procedures, and involvement of new subcontractors, suppliers, or distributors;

(4) changes in sterilization procedures;

(5) changes in packaging; and

(6) changes in the performance or design specifications, circuits parts, components, accessories, ingredients, or physical layout of the device.

Changes in labeling, manufacturing, sterilization, packaging, or performance or design specification which enhance safety of the device or safety in the use of the device may be placed into effect by the sponsor prior to the receipt of a written FDA approval of the supplemental PMA provided:

(1) the submission is plainly marked on the mailing cover and on the supplement "Special PMA Supplement—Changes Being Effected";

(2) the supplemental PMA provides a full explanation of the basis for the changes;

(3) the applicant has received acknowledgement from the Bureau of Medical Devices of receipt of the supplement; and

(4) the supplement specifically identifies the date that such changes are being effected.

Specific examples of changes permitted are:

(1) addition of warnings, contraindications, or side effects;

(2) deletion of misleading, false, or unsupported indications; and

(3) changes in the manufacturing process or quality controls that provide additional assurance of purity, identity, strength, or reliability.

FDA may, as experience permits, issue guidelines listing specific types of changes that do not require FDA approval prior to implementation.

Post-Approval Reports. Continued approval of your device is contingent upon the submission of post-approval reports to the Bureau of Medical Devices at intervals of one year from the date of this letter. The required contents of these reports will be described in the FEDERAL REGISTER in the premarket approval procedural regulation which will be published in the future. Until this regulation is published in final form, each periodic report shall consist of information that previously has not been submitted as part of a PMA or supplemental PMA and which you have obtained since the last post-approval report or since receipt of this letter, whichever is later:

1. A summary and bibliography of reports in the scientific literature involving the device and unpublished reports of *in vitro*, animal and clinical experience studies, investigations, and tests con-

ducted by, reported to, or reasonably available to you involving the device or a related device.

If, after reviewing the summary and bibliography, FDA concludes that it needs a copy of the published and unpublished reports themselves, FDA will notify you that copies of such reports shall be submitted.

2. Written promotional material.

3. A description of changes made in the device not previously submitted in a supplemental PMA.

Adverse Reaction and Device Defect Reporting.

You shall submit a written report to the Bureau of Medical Devices within ten days after you receive or have knowledge of information about:

(1) a mixup of the device or its labeling with another article;

(2) any significant chemical, physical, or other change or deterioration in the device, or any failure of one or more of the devices to meet the specifications established in the application; and

(3) any adverse reaction, side effect, injury, toxicity, or sensitivity reaction or any unexpected incidence, or severity thereof, associated with any clinical use, study, investigation, or test of the device, which has been determined to be attributable to the device or has not been addressed by the device labeling. The term "unexpected" refers to conditions or developments not previously identified in the application.

Note: All conditions of approval are subject to change upon publication of a final premarket approval regulation.